General

Guideline Title

Pemetrexed maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small-cell lung cancer.

Bibliographic Source(s)

National Institute for Health and Care Excellence. Pemetrexed maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small-cell lung cancer. London (UK): National Institute for Health and Care Excellence; 2014 Apr. 45 p. (Technology appraisal guidance; no. 309).

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

Pemetrexed is not recommended for the maintenance treatment of locally advanced or metastatic non-squamous non-small-cell lung cancer (NSCLC) in people whose disease has not progressed immediately following induction therapy with pemetrexed and cisplatin.

People currently receiving treatment initiated within the National Health Service (NHS) with pemetrexed that is not recommended for them by the National Institute for Health and Care Excellence (NICE) in this guidance should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Non-squamous non-small-cell lung cancer

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Internal Medicine

Oncology

Pulmonary Medicine

Intended Users

Advanced Practice Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To assess the clinical effectiveness and cost-effectiveness of pemetrexed maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small-cell lung cancer

Target Population

Patients with locally advanced or metastatic (stage IIIB/IV) non-squamous non-small-cell lung cancer whose disease has not progressed immediately following first-line induction chemotherapy with pemetrexed and cisplatin

Interventions and Practices Considered

Pemetrexed maintenance treatment

Major Outcomes Considered

- Clinical effectiveness
  - Overall survival (OS)
  - Progression-free survival (PFS)
  - Response rates
  - Adverse effects of treatment (according to grade)
  - Health-related quality of life (QoL)
- Cost-effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform an assessment of the manufacturer's submission on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for this technology appraisal was prepared by Liverpool Reviews and Implementation Group (LRiG) (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Critique of the Methods of Review(s)

Searches and Inclusion Criteria

A systematic literature search was conducted to identify relevant Phase 3, randomised controlled trials (RCTs) of pemetrexed as maintenance treatment in people with advanced non-small-cell lung cancer (NSCLC). Key databases were searched, including Ovid Medline, Medline (R) In-Process and EMBASE. The Evidence Based Medicine Reviews database was used to search the Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials and the Cochrane Methodology Register as well as American College of Physicians (ACP) Journal Club, Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment and National Health Service (NHS) Evaluation database. Other databases searched were Biosys Previews and Current Contents. Searches of the American Society of Clinical Oncology website and internal Eli Lilly databases were also undertaken. All searches were conducted up to 25th July 2012. The ERG considers the range of databases included in the search to be thorough. Appropriate search strategies and inclusion criteria were utilised by the manufacturer.

The ERG has conducted its own searches and is confident that the PARAMOUNT trial, as identified by the manufacturer is the only Phase 3 RCT relevant to the decision problem.

Cost-effectiveness

ERG Comment of Manufacturer's Review of Cost-effectiveness

The manufacturer's search was designed to identify studies that evaluated the cost-effectiveness of maintenance treatments for patients with locally advanced or metastatic NSCLC. The search strategy was designed to inform the methodological approach for the economic evaluation and to identify data sources for relevant resources and health effects.

The literature search was performed on 4 February 2011 using National Health Service (NHS) Economic Evaluation Database (NHS EED) and on 7 February 2011 using MEDLINE and EMBASE. Subsequent searches were repeated on 5 October 2011 and 10 September 2012 to update the results. The search strategies used by the manufacturer are provided in the manufacturer's submission (MS).

Hand-searching of retrieved articles and appraisals conducted by NICE was also undertaken by the manufacturer.

Inclusion/Exclusion Criteria

The inclusion and exclusion criteria used by the manufacturer are summarised below.

Parameter	Inclusion Criteria	Exclusion Criteria
Population	Non-small-cell lung cancer (NSCLC) stage IIIB-IV	Study not in the population of interest
Line of therapy	Maintenance treatment	Second-line therapy
Study design	Full economic evaluation (an evaluation of both costs and benefits)	Partial evaluation, cost minimisation, review
Other	Study findings generalisable to the UK population	Duplicates

Number of Source Documents

Clinical Effectiveness

One randomised controlled trial, the PARAMOUNT trial, was identified by the manufacturer.

Cost-effectiveness

Two studies were identified.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform an assessment of the manufacturer's submission on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for this technology appraisal was prepared by Liverpool Reviews and Implementation Group (LRiG) (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Critique of the Methods of Review(s)

PARAMOUNT Quality and Validity Assessment

The manufacturer's quality assessment of the PARAMOUNT trial demonstrates that the trial was well designed with robust methods of randomisation and appropriate blinding. The ERG notes that the primary endpoint was progression-free survival (PFS), but the trial was also powered for overall survival (OS) and that quality of life (QoL) was assessed using the EuroQol 5D (EQ-5D) utility score.

As the trial population was predominantly European, including six centres in the United Kingdom (UK), the results of the trial are considered by the ERG to be applicable to the clinical population in England and Wales, within the limits of the trial population.

Patients were recruited from 83 centres in 16 countries (Australia, Belgium, Canada, Finland, France, Germany, Greece, India, Italy, Netherlands, Poland, Portugal, Romania, Spain, Turkey and the UK). For the results of a trial with so many centres to be meaningfully interpreted, the manner in which the protocol is implemented should be clear and similar across all centres. This is because with so many investigators in different countries, general clinical practice will always be an issue and the results of a trial can only be generalisable if it is executed efficiently. The issue of data quality assurance is addressed in the clinical study report (CSR). It is stated that a number of quality control safeguards were put into place, including, but not limited to, instructional material provided to study sites, investigator training sessions, periodic visits to study sites, contact maintained with study sites, use of standard computer edits to detect errors in data collection. Evidence of study monitoring is provided in the CSR where it is reported that during routine site monitoring, Eli Lilly identified 17 events described as 'extraordinary', 'serious and/or persistent issues' that would not have been picked up from the electronic reporting forms. Once identified, the CSR states that each issue was addressed and documented.

According to the CSR, a total of 69 (19.2%) patients randomised to pemetrexed plus best supportive care (BSC) and 27 (15.0%) patients randomised to placebo plus BSC had a protocol deviation. Table 7 in the ERG report summarises the protocol deviations that occurred. Levels of protocol deviations were low and most were comparable across the two treatment arms and so this is not of great concern to the ERG.

PARAMOUNT Trial Description and Critique of the Statistical Approach

The PARAMOUNT trial consisted of two phases; the first phase was a non-randomised induction phase and the second was a double-blind randomised maintenance phase.

According to the published paper and the statistical analysis plan (SAP), patients were randomised (2:1) to receive treatment using a computer generated random sequence with a block size of three. The trial report states that the "randomisation ratio was chosen to provide sufficient comparative data to show the superiority of pemetrexed plus BSC while reducing patient exposure to the potentially inferior treatment of placebo plus BSC." Randomisation was stratified with the following baseline and prognostic factors:

- Eastern Cooperative Oncology Group (ECOG) performance status just before randomisation (0 vs 1)
- Tumour response to induction chemotherapy (CTX) (complete or partial response vs stable disease)
- Disease stage before administration of induction therapy (IIIB vs IV)

In the published paper it is stated that randomisation was done using the Pocock and Simon minimisation method; however the ERG found no mention of minimisation in other documents that described the PARAMOUNT trial methodology. In their clarification response to the ERG, the manufacturer stated that minimisation was not used. The ERG is unclear as to why the main published report of the trial refers to the Simon and Pocock minimisation method but is satisfied with the method of randomisation.

Statistical Analyses

According to the manufacturer's submission (MS), the analysis population for primary and secondary efficacy analyses was the intention-to-treat (ITT) population, defined as all patients randomised to maintenance treatment, whether or not study treatment was received, analysed according to the treatment assigned at randomisation. The analysis population for the safety analysis was all patients enrolled in the study that were treated with at least one dose of pemetrexed plus cisplatin during the induction phase.

The statistical methods used to analyse the efficacy outcomes in the PARAMOUNT trial are presented in Table 10 in the ERG report. The ERG is satisfied that in the main, these methods of analysis are appropriate, however the ERG notes that in the MS p-values are reported in relation to adverse events (AEs), suggesting that hypothesis tests were performed although no formal statistical analysis of AEs was specified in the SAP.

See Section 4 in the ERG report for additional information on the statistical analyses (see the "Availability of Companion Documents" field).

Meta-analysis

As only one RCT investigating the efficacy of pemetrexed is available, it was not possible to perform a meta-analysis.

See Section 4 in the ERG report for additional information on clinical effectiveness analysis (see the "Availability of Companion Documents" field).

Cost-effectiveness

Summary and Critique of Manufacturer's Review of Cost-effectiveness Evidence

Model Structure

A schematic of the manufacturer's model is shown in Figure 3 in the ERG report. It comprises three health states: pre-progression, post-progression and dead. All patients enter the model in the pre-progression health state following a course of pemetrexed plus cisplatin CTX. At the beginning of each time period patients can either remain in the same health state or progress to a 'worse' health state, i.e., move from pre-progression to post-progression or dead; or move from post-progression to dead.

The resource use and utilities applied in the pre-progression health state relate to the maintenance phase of treatment. The post-progression health state corresponds with National Health Service (NHS) clinical practice following disease progression, representing the time period after maintenance treatment until death. On entering this state clinicians and patients reassess treatment options and a patient may be offered second-line treatment.

Variants of this model structure have been used frequently in the modelling of metastatic oncology for NICE Single Technology Appraisals (STAs).

The model has been developed in Microsoft Excel and has a 21-day cycle length. It employs a continuity correction and the base-case time horizon is 15.99 years. A discount rate of 3.5% has been used for both costs and outcomes and the perspective is stated to be that of the NHS and Personal Social Services.

See Section 5 in the ERG report for more information on the cost-effectiveness analysis (see the "Availability of Companion Documents" field).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Care Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE Web site. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who Is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

Summary of Appraisal Committee's Key Conclusions

Availability and Nature of Evidence

The manufacturer submitted a state-transition Markov model to evaluate the cost-effectiveness of pemetrexed compared with placebo.

Uncertainties Around and Plausibility of Assumptions and Inputs in the Economic Model

The Committee was not persuaded by the manufacturer's approach to the modelling of progression-free survival and overall survival.

The Committee also concluded that more accurate estimates of resource use and utility parameters were available than those used in the manufacturer's revised base case.

Incorporation of Health-Related Quality-of-Life Benefits and Utility Values. Have Any Potential Significant and Substantial Health-Related Benefits Been Identified That Were Not Included in the Economic Model, and How Have They Been Considered?

Patients in PARAMOUNT were asked to rate their health condition using the EuroQol 5D (EQ-5D). The manufacturer noted that the trial data did not provide values suitable for the pre- and post-progression health states, therefore a mixed regression analysis was carried out.

No significant and substantial health-related benefits that have not been captured by the quality adjusted life year (QALY) calculation were identified either in the submission or at the Committee meeting.

Are There Specific Groups of People for Whom the Technology Is Particularly Cost Effective?

No clinically relevant subgroups were identified during the appraisal.

What Are the Key Drivers of Cost-effectiveness?

The different approaches to estimating overall survival for the lifetime of the model between the manufacturer's updated revised base case (incremental cost-effectiveness ratios [ICERs] of £58,918 to £68,771 per QALY gained) and the Evidence Review Group's (ERG's) revised analysis (approximately £74,500 per QALY gained).

Most Likely Cost-effectiveness Estimate (Given as an ICER)

The Committee considered that the most plausible ICER was approximately £74,500 per QALY gained.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

Consultee organisations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

The Appraisal Committee considered clinical and cost-effectiveness evidence submitted by the manufacturer of pemetrexed and a review of this submission by the Evidence Review Group.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of pemetrexed maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small-cell lung cancer

Potential Harms

The Summary of Product Characteristics reports that the most common adverse reactions of pemetrexed are bone marrow suppression manifested as anaemia, neutropenia, leukopenia, thrombocytopenia; and gastrointestinal toxicities, manifested as anorexia, nausea, vomiting, diarrhoea, constipation, pharyngitis, mucositis, and stomatitis.

For full details of adverse reactions, see the Summary of Product Characteristics.

Contraindications

Contraindications

For full details of contraindications, see the Summary of Product Characteristics.

Qualifying Statements

Qualifying Statements

- This guidance represents the views of the National Institute for Health and Care Excellence (NICE) and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Mobile Device Resources

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report

Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

National Institute for Health and Care Excellence. Pemetrexed maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small-cell lung cancer. London (UK): National Institute for Health and Care Excellence; 2014 Apr. 45 p. (Technology appraisal guidance; no. 309).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2014 Apr

Guideline Developer(s)

National Institute for Health and Care Excellence (NICE) - National Government Agency [Non-U.S.]

Source(s) of Funding

National Institute for Health and Care Excellence (NICE)

Guideline Committee

Appraisal Committee

Composition of Group That Authored the Guideline

Committee Members: Professor Gary McVeigh (*Chair*), Professor of Cardiovascular Medicine, Queens University Belfast and Consultant Physician, Belfast City Hospital; Dr Lindsay Smith (*Vice Chair*), General Practitioner, West Coker Surgery, Somerset; Professor Darren Ashcroft, Professor of Pharmacoepidemiology, School of Pharmacy and Pharmaceutical Sciences, University of Manchester; Dr Aomesh Bhatt, Director of Regulatory and Medical Affairs, Europe and North America, Reckitt Benckiser; Dr Andrew Black, General Practitioner, Mortimer Medical Practice, Herefordshire; Professor David Bowen, Consultant Haematologist, Leeds Teaching Hospitals NHS Trust; Dr Matthew Bradley,

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Financial Disclosures/Conflicts of Interest

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site .

Availability of Companion Documents

The following are available:

- Pemetrexed for maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous and non-small-cell lung cancer (TA309). Costing statement. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Apr. 1 p. (Technology appraisal guidance; no. 309). Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site .
- Greenhalgh J, Bagust A, Blundell M, Dwan K, Beale S, Davis H, Dundar Y, Vecchio F, Sacco J, Marshall E. Pemetrexed for maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small cell lung cancer. Liverpool (UK): LRiG, University of Liverpool; 2012. 75 p. Electronic copies: Available in Portable Document Format (PDF) from the NICE Web site .

Patient Resources

The following is available:

- Pemetrexed as maintenance treatment for non-small-cell lung cancer after pemetrexed and cisplatin. Information for the public. London

(UK): National Institute for Health and Care Excellence (NICE); 2014 Apr. (Technology appraisal guidance; no. 309). Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site . Also available for download as an eBook or ePub from the NICE Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This NGC summary was completed by ECRI Institute on June 29, 2014.

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